Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claim 1 has been amended. Claims 7-23 have been withdrawn from further consideration as being drawn to non-elected species. New claims 24-27 have been added.

Written descriptive support for the amendment of claim 1 is found at paragraph [0036], [0037], [0039], [0040], [0042], [0043], [0045], and [0046] of the specification. Descriptive support for new claims 24-27 is found at paragraphs [0038], [0039], [0040], and [0045]. No new matter has been added.

In the response to the restriction and election of species requirement filed on February 25, 2009, applicant elected the method of Group A (i.e. claims 1-11 and 22-23) and tiotropium bromide as the species. This response stated that claims 1, 6, 22, and 23 read on the elected species; however, after a review of the outstanding office action, it is believed that claims 2-5 also read on the elected species. Accordingly, applicant submits that claims 2-5 should also now be examined.

Urinary incontinence afflicts a large and diverse patient population. The United States Department of Health and Human Services Agency for Health Care Policy and Research (AHCPR) reviewed the literature on the incidence of urinary incontinence, including the clinical, psychological, and social impact of the disorder, as well as monetary costs to society. The 1996 AHCPR study estimated that 13 million Americans are incontinent; of these, 11 million are women. One in four women ages 30-59 has experienced an episode of urinary incontinence, and 50% or more of the elderly persons living at home or in long-term care facilities are incontinent. $16.4 billion is spent every year on incontinence-related care: $11.2 billion for community-based programs and at home, and $5.2 billion in long-term care facilities. $1.1 billion is spent every year on disposable products for adults.

Twenty-nine investigators from 10 countries gathered in San Francisco in June, 2003, at an international symposium sponsored by The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to discuss the current understanding of risk factors and treatment outcomes for incontinence in women. The NIDDK Symposium participants revealed the following facts. The estimated cost of incontinence increased by 250% over 10 years, an amount greater than can be accounted for by medical inflation. Other countries are experiencing this phenomenon as well. In Sweden, for example, the cost of incontinence was estimated as 1.8 billion Swedish crowns (1990 SEK, equivalent to $400

million 1995 U.S. dollars). The elderly account for more than two thirds of the cost of incontinence in the U.S., and costs are expected to increase with the increasing proportion of elderly in society.

A multitude of recent publications further highlight the rising cost to society associated with the management of incontinence and other bladder disorders.

Contraction of the bladder detrusor muscle is mediated by cholinergic muscarinic receptors. Muscarinic receptors are divisible into several subtypes (M_1-M_5 for humans, m_1-m_5 for animals and other cells) that are distinguishable based on binding of selective ligands. These muscarinic receptor subtypes exist in differing concentrations in different tissues.

The present invention targets muscarinic receptors by administration of novel antimuscarinic agents via a catheter to the bladder to attain prolonged maintenance of bladder control in otherwise incontinent patients while minimizing systemic side effects of the medication.

The drug oxybutinin chloride (4-diethylamino)2-butynyl-cc-cyclohexyl-a-hydroxybenzeneacetate HCl; trade name Ditropan®) is a standard antimuscarinic therapeutic agent for urinary incontinence. Relief of symptoms in neurogenic bladder disorders is thought to result from its combined antimuscarinic, antispasmodic, and local anesthetic activities. However, antimuscarinic medications are associated with side effects, including dry mouth and cognitive impairment, limiting its acceptability to many patients. These side effects are, at least, unpleasant, and may be intolerable when taken in combination with other medications commonly used by the elderly. In fact, use of oral oxybutynin is frequently discontinued because of the unpleasantness of the side effects.

For treatment of detrusor overactivity, AHCPR 1992 (since reissued with revisions) recommended oxybutynin at oral doses of 2.5-5 mg/kg, to be taken 3-4 times per day. At the time of agency review, 5 of 6 randomized controlled studies reported superiority of oxybutinin to placebo. One exception was a study of elderly nursing home residents that used less frequent administration of the drug.

The dose-related antimuscarinic side effects of oral oxybutynin include marked xerostomia, dry skin, blurred vision, nausea, and constipation. Severe mouth dryness occurred in 84% of subjects receiving 5 mg/kg four times/day (AHCPR, 1992). Side effects could be minimized by administration of this compound via clean intermittent self-catheterization directly into the bladder (intravesical administration). However, this

required at least daily self-catheterization. Better restoration of bladder control required multiple catheter insertions each day. A series of papers reported beneficial effects in different patient groups.

A double-blind, randomized, placebo-controlled parallel group study of intravesical oxybutynin was reported in which there was some systemic absorption of the drug following intravesical administration, but the incidence of adverse side effects was low, which reported that instillation of the drug two to three times daily via clean self intermittent catheterization resulted in 21% of the patients dropping out due to inability to tolerate the catheterization or difficulty in retaining the drug solution in the bladder.

U.S. Patent No. 5,001,160 to McPherson et al. describes antimuscarinic agents for the treatment of neurogenic bladder disease. The compounds disclosed were said to have longer durations of action than older anticholinergic agents such as methantheline and propantheline. The majority of neurogenic bladder patients have spastic or hypertonic conditions. Clinicians generally aim to convert this condition to hypotonia as a way to treat the primary problem of incontinence. Thus, when the condition has been "converted" to hypotonia, it can be managed in a straightforward way by intermittent catheterization. For those patients who cannot be converted from the hypertonic to the hypotonic state and who still need to urinate every hour, longer term treatment with muscarinic receptor antagonists (loosely called anticholinergics) was said to be necessary. As noted above, the current drug of choice for this treatment modality is oxybutynin, which is considered to be better than the older anticholinergics. 1-aryl-l-hydroxy-l-R,-3-(4-R,-I-piperazinyl)-2-propanones can be used for treatment of bladder disease. In preferred compounds, R_1 was a cycloalkyl of 3-6 carbons, most preferably cyclohexyl or cyclobutyl. R_2 was lower alkyl, benzyl, para-substituted benzyl or cinnamyl. The most preferred compound was 1-cyclobutyl-l-hydroxy-l-phenyl-3-(4-benzyl-l-piperazinyl)-2-propanone. For parenteral administration, the compounds were prepared in conventional aqueous injection solutions. Extemporaneous injection solutions could be prepared from sterile pills, granules or tablets, and contained diluents, dispersing and surface active agents, binders, and lubricants, as well as the anticholinergic compound. Tolterodine is a new antimuscarinic of comparable duration of action which is reported to cause a lower incidence of dry mouth (~9%). The following dose-related side effects were observed with tolterodine: diminished stimulated salivation after 3.2 mg, increased heart rate after 6.4 mg, and altered the nearpoint of vision after 12.8 mg. Six of 8 subjects reported micturition difficulties after a dose of 12.8 mg.

Terodiline has both anticholinergic and calcium antagonist properties, and effectively reduces abnormal bladder contractions caused by detrusor instability. When administered to adult patients with urge incontinence (generally as a 25 mg dose twice daily), terodiline reduced micturition frequency and incontinence episodes. Bladder volume at first urge and bladder capacity were increased. Children with diurnal enuresis respond similarly to a daily 25 mg dose. Terodiline at 50 mg/day was said to be preferred by patients when compared with emepronium 600 mg/day or flavoxate 600 mg/day, and tended to reduce voluntary micturition frequency and episodes of incontinence more effectively than these other drugs. Anticholinergic side effects were the most common ones reported.

Anhydroecgonine methyl ester (AEME), the primary pyrolysis product of cocaine, is structurally similar to arecoline and anatoxin A. While investigating the effects of crack smoking, it was noted that experimental animals frequently showed bronchoconstriction.

This observation led to a focus on AEME and other anhydroecgonine esters (AEE) as bronchoconstrictors when given by inhalation. When this agent was studied in isolated guinea pig tracheal rings, it was found unexpectedly (in view of the bronchoconstricting action of cocaine), that AEME lacked cholinergic agonist activity in this tissue and in detrusor muscle *in vitro*. Subsequently, some agonistic effects were demonstrated at high doses in sheep consistent with action at the M_2 muscarinic receptors.

Even more surprisingly, AEME turned out to be a potent non-competitive muscarinic antagonist *in vitro*.

The antagonistic effects were insurmountable even with the addition of increasing amounts of acetylcholine (ACh). Furthermore, the anticholinergic effects were irreversible, so that tissue exposed to AEME could not later attain its original magnitude of contraction. These *in vitro* findings were unexpected because AEME, resembling arecoline and anatoxin in structure, was expected to behave as a cholinergic agonist. AEE compositions, derivatives or analogues thereof having anticholinergic activity, methods of preventing or inhibiting cholinergic responses, and methods of using the compositions to prevent or treat diseases associated with bronchoconstriction have been described.

Note that some effects were subsequently demonstrated at high doses of this interesting compound that are consistent with agonist activity at the m_2 muscarinic receptor in sheep, as well as effects in guinea pigs.

Interstitial cystitis (IC), a syndrome occurring primarily in women, is characterized by urinary urgency and frequency, suprapubic pain, and petechial bladder mucosal hemorrhages upon distention under general anesthesia. Almost 50% of IC patients also suffer from allergies and irritable bowel syndrome, all of which are exacerbated by stress. One of the prevailing theories to explain IC pathophysiology is the increased number of activated mast cells in the bladder. Mast cells mediate hypersensitivity reactions wherein they are triggered by immunoglobulin E (IgE) and antigen (allergen) to release numerous vasoactive anproinflammatory substances. Mast cells are found in juxtaposition to neurons and are also activated by direct nerve stimulation, as well as by ACh, neurotensin, and Substance P. Barbalias, GA, "Interstitial Cystitis: Bladder Training with Intravesical Oxybutynin," *J. Urol.* 163:1818-1822 (2000), demonstrated that intravesical administration of oxybutynin to women with interstitial cystitis resulted in an improvement in their signs and symptoms that was better than the improvement produced by simple expansion of the bladder with saline.

In addition to its role in bladder control, the parasympathetic nervous system plays a major role in regulating bronchomotor tone. One drug used to treat respiratory disease, such as asthma, is the quaternary anticholinergic agent isopropylatropine bromide, also called ipratropium bromide (Atrovent®). This agent, administered by inhalation, is poorly absorbed so that it exerts its effects primarily, and in a limited manner, on the internal surfaces of the lungs. Thus, a major advantage of ipratropium for respiratory therapy is the possibility of reaching elevated regional tissue (e.g., lung) concentrations with few systemic anticholinergic effects. Another advantage of ipratropium compared to other anti-asthmatic drugs is its duration of action. Its pharmacologic effect becomes maximal in about an hour, and persists for several hours. A compound with these features may also be useful for long duration therapy of bladder disease.

Thus, antimuscarinic therapies are widely used for treatment of bladder diseases, but they are fraught with side effects, which not only limit their acceptance by patients, but also complicate medical management. What are needed are effective methods of treating bladder disease without the unpleasant side effects associated with the current standard therapeutics.

The rejection of claims 1, 6, 22, and 23 under 35 U.S.C. § 102(e) as anticipated by WO 02/45711 to Bannister et al. ("Bannister") is respectfully traversed in view of the above amendments.

Bannister relates to the simultaneous, sequential, or separate use of an anti-muscarinic agent and a calcium channel blocker in the treatment of a muscle tone disorder or a proliferative, inflammatory, or secretory condition. Anti-muscarinic agents that can be used in this invention include tiotropium. Bannister also discloses that the active agent may be used in therapy where the condition to be treated involves urinary incontinence. Bannister discloses topical use of anti-muscarinic agents either dermally to the lung or to the gastrointestinal tract. However, Bannister fails to mention or suggest administering anti-muscarinic agent intravesically as required by the claimed invention.

The significance of the difference in the modes administration by Bannister and the present invention is demonstrated by the ability of the claimed intravesical application treatment to prolong the duration of action of the anti-muscarinic agent, a benefit no where mentioned in Bannister. This results because the compounds used in the present invention, when topically applied in the bladder, are minimally distributed beyond the tissue surface and immediately underlying tissue. These compounds tend to be stored in the bladder lining due to an attraction between the positive charge of the compounds and the negative charge of the sulfated sugars comprising glycosaminoglycan layer lining the bladder. This local maintenance of medication prolongs its action on the bladder. Accordingly, Bannister neither teaches nor suggests the claimed invention.

Therefore, the rejection of claims 1, 6, 22, and 23 for anticipation is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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/Michael L. Goldman/
Michael L. Goldman
Registration No. 30,727

NIXON PEABODY LLP
1100 Clinton Square
Rochester, New York 14604-1792
Telephone: (585) 263-1304
Facsimile: (585) 263-1600